PUBLIC ASSESSMENT REPORT
Scientific Discussion

TELMISARTAN RATIOPHARM
TELMISARTAN RATIOPHARM GENERIQUES
TELMISARTAN RATIO
20 mg, 40 mg and 80 mg
Tablets
(Telmisartan)

FR/H/398/01-03/DC
FR/H/399/01-03/DC
FR/H/400/01-03/DC

Applicant: Ratiopharm GmbH

Date of the PAR: December 2010
1. INTRODUCTION

Based on review of the quality, safety and efficacy data, the Afssaps has granted a marketing authorisation (MA) for TELMISARTAN Ratiopharm 20 mg, 40 mg and 80 mg tablets, TELMISARTAN Ratiopharm Génériques 20 mg, 40 mg and 80 mg tablets, TELMISARTAN Ratio 20 mg, 40 mg and 80 mg tablets from Ratiopharm GmbH on 7th September 2010.

Note: Telmisartan is used throughout the PAR also to indicate all the associated names.

Telmisartan is indicated in:

Hypertension: Treatment of essential hypertension in adults.

Cardiovascular prevention: Reduction of cardiovascular morbidity in patients with:
- manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or
- type 2 diabetes mellitus with documented target organ damage

A comprehensive description of the indications and doses is given in the SmPC.

These decentralised procedure applications concern a generic medicinal product of Micardis 20 mg, 40 mg and 80 mg registered by Boehringer Ingelheim International GmbH since 1998 through a centralised procedure.

No new preclinical or clinical studies were conducted, which is acceptable for this kind of application.

Two bioequivalence studies are submitted to show the bioequivalence between Telmisartan 20 mg and 80 mg tablets and the reference product.

During the procedure, a potential serious risk to public health concerns was raised regarding the restricted part of ASMF but this issue was resolved by adequate responses of the applicant at D190.

The procedure was ended positively on 16th June 2010.

2. QUALITY ASPECTS

2.1 Introduction

The medicinal product is presented in the form of tablet containing three different strengths, i.e. 20 mg, 40 mg and 80 mg of telmisartan.

The excipients are Sodium Hydroxide, Hydroxypropyl-methylcellulose 3 cP, Sorbitol, Povidone K-90, Meglumine, Mannitol, Magnesium Stearate, and Purified Water (not present in the finished product).

Telmisartan Tablets are packed in two different types of packs (Aluminium/ aluminium blister and white HDPE containers and PP closures with desiccant).
2.2 Drug substance

Telmisartan has a monograph in the Ph.Eur. The Active Substance Master File (ASMF) procedure is used for the active substance. Telmisartan is a white or slightly yellowish, crystalline powder which is insoluble in water. The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated. Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

2.3 Medicinal product

Telmisartan tablets are formulated using excipients described in the current Ph Eur. All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01). The development is sufficiently described in accordance with the relevant European guidelines. Comparative in vitro dissolution profiles and impurities profiles of the generic product and the reference product support the essentially similar character. The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification. The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose. Stability studies under ICH conditions have been performed. The data support the shelf life claimed in the SPC, 3 years with no special storage precautions.

3. NON-CLINICAL ASPECTS

3.1 Discussion on the non-clinical aspects

Since this product is a generic application of a widely used and well known substance based on a full application with regard to preclinical data, no further data have been submitted or are considered necessary, which is adequate. Pharmacodynamic, pharmacokinetic and toxicological properties of telmisartan are well known. No modification of section 5.3. Preclinical Safety Data of the SmPC was necessary; the initial Applicant’ proposal was endorsed by the RMS and all CMS.

Environmental risk

The product is intended as a substitute for identical products on the European market. Evaluation of the potential environmental risk posed by the medicinal product has not been provided. The approval of this product does not result in an increase of the total quantity of telmisartan released into the environment. It does not contain any component which results in additional hazard to the environment during storage, distribution, use and disposal.
4. CLINICAL ASPECTS

4.1 Introduction
As all clinical data concerning telmisartan have already been evaluated, this application consists essentially in the demonstration of the bioequivalence between telmisartan generic and the innovator. Telmisartan is a well-known active substance with established efficacy and tolerability.

4.2 Discussion on the clinical aspects
Telmisartan is a nonpeptide, benzimidazole-derivative angiotensin II receptor, type 1, antagonist or blocker (ARB) which selectively and competitively blocks the angiotensin II type 1 (AT1) receptor, which mediates the vasopressor and aldosterone effects of angiotensin II (AT).

Telmisartan, like the ARB prototype losartan, interrupts most functions of the RAS by preventing the interaction of its critical effector AT with AT1-receptors as a highly selective, directly acting (non-prodrug), and competitive antagonist. Blockade of AT actions has found therapeutic application in the treatment of hypertension, HF, myocardial infarction and diabetic nephropathy. The effects of AT are exerted through specific cell surface receptors of which two, the AT1- and AT2-receptor, have been identified. Most of the biological effects of AT are mediated by the AT1-receptor.

Therapeutic indications
Treatment of essential hypertension.
Cardiovascular prevention
Reduction of cardiovascular morbidity in patients with:
- manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or
- type 2 diabetes mellitus with documented target organ damage

Pharmacovigilance System (PV System) and Risk Management Plan (RMP)
Pharmacovigilance System
As described, the PV System adequately covers all the requested information, including: i) the qualified person responsible for pharmacovigilance (including the backup procedure to apply in the absence of the EUQP), ii) the documented procedures; iii) databases; iv) training and v) the documentation (including the locations of the different types of pharmacovigilance source documents, and archiving arrangements).

Risk Management Plan
In view of the existing knowledge and experience with the active substance telmisartan, the available data and the known risk benefit profile, a specific RMP is not justified. Routine Pharmacovigilance with adequate Pharmacovigilance System as described and completed by the applicant are sufficient to adequately follow up the safety profile of telmisartan.

4.3 Pharmacokinetics
Two bioequivalence studies were provided to support the application.

4.3.1 Bioequivalence Study with 20 mg Tablet: Study DEV 248201-1TEL06
The study was designed according to an open-label, randomised, single-dose, 2-way crossover, 2-sequence classical scheme. 54 healthy non-smoking adult female and male volunteers were enrolled. Subjects were divided in two groups for dosing. A total of 52 subjects completed the clinical phase of the study.
Test and reference products:
- **Test product**: Telmisartan 20 mg tablets, manufactured by Ratiopharm India Pvt. Ltd, India. This batch is clearly described.
- **Reference product**: Micardis 20 mg tablets, manufactured by Boehringer Ingelheim GmbH, Germany.

The pharmacokinetic analysis was performed on ln-transformed AUC0-t, AUC0-∞ and Cmax was carried out. The statistical model included sequence, period and treatment factors as fixed effects and subject within sequence as random effect.

A non parametric test (Wilcoxon’s Signed-Rank test) was carried out to compare Tmax.

**Results:**

**Telmisartan**: Pharmacokinetic parameters (AUC and Cmax: arithmetic mean ± SD, tmax: median, range): Single 75 mg oral dose.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC0-t (ng*h/ml)</th>
<th>AUC0-∞ (ng*h/ml)</th>
<th>Cmax (ng/ml)</th>
<th>tmax (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(S.D.)</td>
<td>413.92 (291.94)</td>
<td>455.80 (321.19)</td>
<td>18.35 (8.19)</td>
<td>3 (0.33-12)</td>
</tr>
<tr>
<td><strong>Reference</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(S.D.)</td>
<td>396.37 (256.46)</td>
<td>436.93 (286.87)</td>
<td>18.49 (10.97)</td>
<td>1 (0.33-12)</td>
</tr>
<tr>
<td><strong>Ratio (90% CI)</strong></td>
<td>[97;106]%</td>
<td>[97;107]%</td>
<td>[96;114]%</td>
<td></td>
</tr>
<tr>
<td><strong>Point estimate</strong></td>
<td>101.7 %</td>
<td>101.8 %</td>
<td>104.4 %</td>
<td></td>
</tr>
<tr>
<td><strong>Intra-subject CV (%)</strong></td>
<td>13.6 %</td>
<td>15.3 %</td>
<td>26 %</td>
<td></td>
</tr>
</tbody>
</table>

The conventional CI for Log transformed AUCt, AUCinf and Cmax are within the [80; 125]% acceptance range. No significant difference in Tmax was evidenced by the non parametric test. Therefore, the BE of the test and reference drug products could be concluded.

**4.3.2 Bioequivalence Study with 80 mg Tablet: Study DEV248202-2TEL06.**

The study was designed according to an open-label, randomised, single-dose, 2-way crossover, 2-sequence classical scheme. 46 healthy non-smoking adult female and male volunteers were enrolled. A total of 43 subjects completed the clinical phase of the study.

**Test and reference products:**
- **Test product**: Telmisartan 80 mg tablets, manufactured by Ratiopharm India Pvt. Ltd, India. This batch is clearly described.
- **Reference product**: Micardis 80 mg tablets, manufactured by Boehringer Ingelheim GmbH, Germany.

The pharmacokinetic analysis was performed on ln-transformed AUC0-t, AUC0-∞ and Cmax was carried out. The statistical model included sequence, period and treatment factors as fixed effects and subject within sequence as random effect. A non parametric test (Wilcoxon’s Signed-Rank test) was carried out to compare Tmax.
Results:

Telmisartan: Pharmacokinetic parameters (AUC and Cmax: arithmetic mean ± SD, tmax: median, range): Single 75 mg oral dose.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t}</th>
<th>AUC_{0-\infty}</th>
<th>C_{max}</th>
<th>t_{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1752.88 (1347.5)</td>
<td>2055.01 (1749.5)</td>
<td>248.10 (176.8)</td>
<td>1.25 (0.5-4)</td>
</tr>
<tr>
<td>Reference</td>
<td>1807.76 (1457.45)</td>
<td>2103.68 (1825.85)</td>
<td>264.61 (200.82)</td>
<td>1 (0.33-4)</td>
</tr>
</tbody>
</table>

*Ratio (90% CI) Point estimate

| Intra-subject CV (%) | 15.02 % | 13.74% | 40.38 % |

AUC_{0-\infty} area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration: median, min and max

*log-transformed values

The conventional CI for Log transformed AUC_t, AUC_{\infty} and C_{max} are within the [80; 125]% acceptance range. No significant difference in T_{max} was evidenced by the non-parametric test. Therefore, the BE of the test and reference drug products could be concluded.

5. OVERALL DISCUSSION , BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Satisfactory chemical-pharmaceutical documentation has been provided, assuring consistent and sufficient quality of the product.

Considering the extensive knowledge on the preclinical and clinical data for telmisartan, and given human experience, it can be stated that the telmisartan tablets do not raise any new pre-clinical or clinical concerns.

Based on the submitted bioequivalence studies, the telmisartan tablets are considered bioequivalent with the reference product.

Following Day 120, the SmPC and PL were amended to implement information regarding an indication extension in the prevention of the cardiovascular morbidity based on the results of ONTARGET, TRANSCEND and PRoFESS Studies, in line with the last version of the innovator MICARDIS (EMEA/H/C/209/II/73).

In conclusion, the Concerned Member States mutually recognised the French evaluation of the marketing authorisation; all issues being solved for the marketing authorisation of Telmisartan 20 mg, 40mg and 80 mg tablets.

There was no discussion at the CMDh.
The following post-approval commitments were made during the procedure regarding Quality:

1) to remove breakline on the 20 mg tablet.
2) to carry out a complete process validation on the first three consecutive full-scale production batches of each strength according to the submitted validation protocol before placing this size on the market.

The current SmPC, Package Leaflet (PL) and labelling are in the agreed template.

User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was German. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The test consisted of: a pilot test, followed by two rounds with 20 participants. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.